Treatment of Hypertension

Dr. Ghada Farouk Saleh

Assistant professor of Medical Pharmacology

Internal medicine specialist/ CU

Cardiopulmonary module

INTENDED LEARNING OBJECTIVES (ILO)

Lecture 4:

1. Identify the role of sodium nitroprusside (mixed dilator) in the treatment of hypertension, its side effects and how to prevent.
2. Identify the role of labetalol, diazoxide, Fenoldopam in the treatment of hypertension

3. Discuss the pharmacology of drugs used in the treatment of hypertensive urgency and emergency

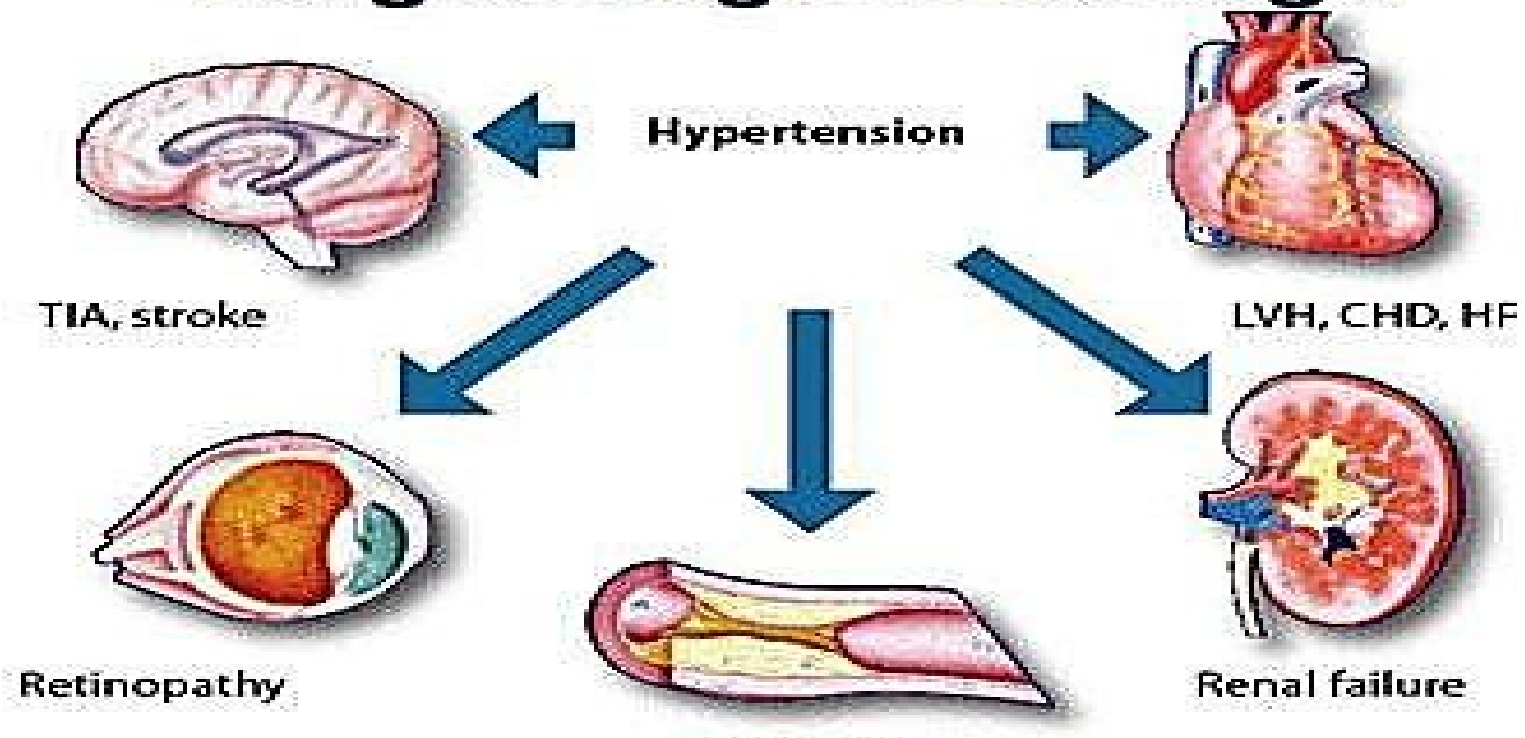
Classification:

- Hypertensive urgency
  - Rapid rise of BP to 180/120mmHg → not associated with organ damage.

- Hypertensive emergency
  - Rapid rise of BP to 180/120mmHg → associated with organ damage (brain, heart, kidney)

- Malignant hypertension

Complications of Hypertension: Target-Organ Damage



TIA, transient ischemic attack; LVH, left ventricular hypertrophy; CHD, coronary heart disease; HF, heart failure

medscape

(2013 ESH/ESC Guidelines for the management of arterial hypertension)

Hypertensive urgencies

BP > 180/120 without TOD

Management :

-No need for hospital admission .(no TOD)

-Management : in ER or outpatient clinic or a

-Gradual reduction of BP .

- Oral drugs are used to lower BP within 24 hours

-The following **oral** agents are used

Loop diuretics

Vasodilators

Labetalol

B-blockers

Clonidine

Captopril

Hypertensive emergency

Hypertensive emergency is a rare but life-threatening situation

BP > 180/120 with TOD

Management:

1- ICU admission

2- Reduction of BP :

To approximately 100 mmHg Diastolic

within 1 hour

Hypertensive emergencies

Drugs used in hypertensive emergencies :

Use rapidly acting **Parenteral** antihypertensive drugs as: **Route : I.V.**

Vasodilators:

- Na Nitroprusside IV infusion (Direct Arteriovenodilator)
- Nitroglycerine IV infusion (Direct Venodilator)
- Diazoxide IV (**D**irect Arteriodilator)
- Hydralazine IV (**D**irect Arteriodilator)

Diuretics:

- Furosemide IV (Loop Diuretic)

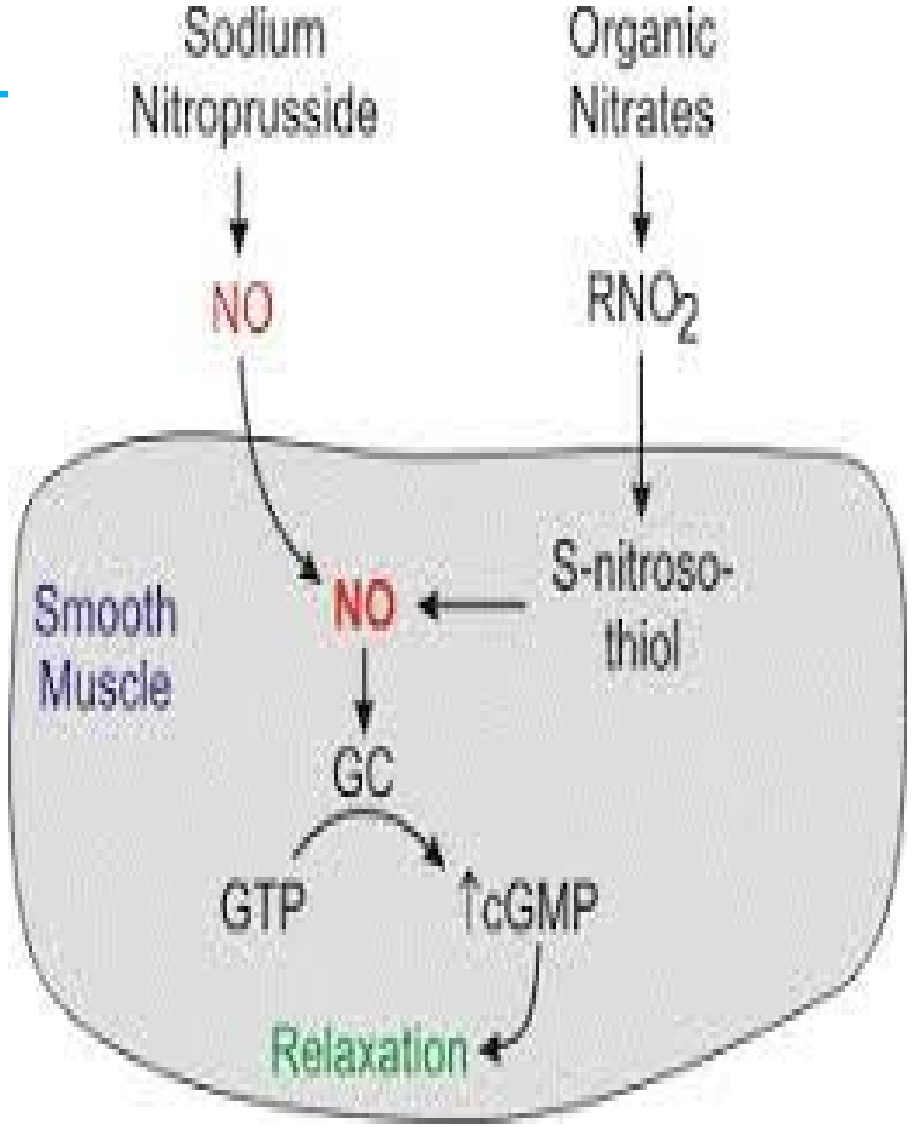
Sympatholytics:

- Methyldopa IV (**α-2** agonist).

Fenoldopam IV infusion: Dopamine D-1 receptor agonist

1. Sodium Nitroprusside

1. The action occurs as a result of activation of **guanylyl cyclase**, either via release of nitric oxide or by direct stimulation of the enzyme. The result is increased intracellular cGMP, which relaxes vascular smooth muscle
2. Mixed dilator: acts equally on arterial and venous smooth muscle (mixed arteriolar & venular vasodilator)
3. *It* causes vasodilation with reflex tachycardia



Pharmacokinetics

a- Used by **IV Infusion**. Onset:1/2 min. Peak:2 min. Duration: 3 min.
b- Nitroprusside: RBCs & Endothelium: NO + Cyanide.
c- Cyanide by Liver Rhodanese enzyme: Thiocyanate.
d- Thiocyanate is excreted in urine.

Disadvantages of Nitroprusside

a- Large dose: Severe Hypotension & Shock.
b- Sudden Stop: Rebound Hypertension.
c-Prolonged Use especially in old age: Accumulation of:
-Cyanide: Acidosis & arrhythmia: DEATH (Add Thiosulfate or Hydroxocobalamine)
Thiocyanate: Delirium & Psychosis.
d-Teratogenic.

Therapeutic Uses of Nitroprusside:

a- Emergency Hypertension e.g. Hypertensive Encephalopathy.
b- Emergency Heart Failure (Acute left ventricular failure & Pulmonary Edema).
c- Controlled hypotension during plastic & neuro-surgery.
d- Acute aortic dissecting aneurysm (with β-Blockers).

Precautions during Nitroprusside infusion:

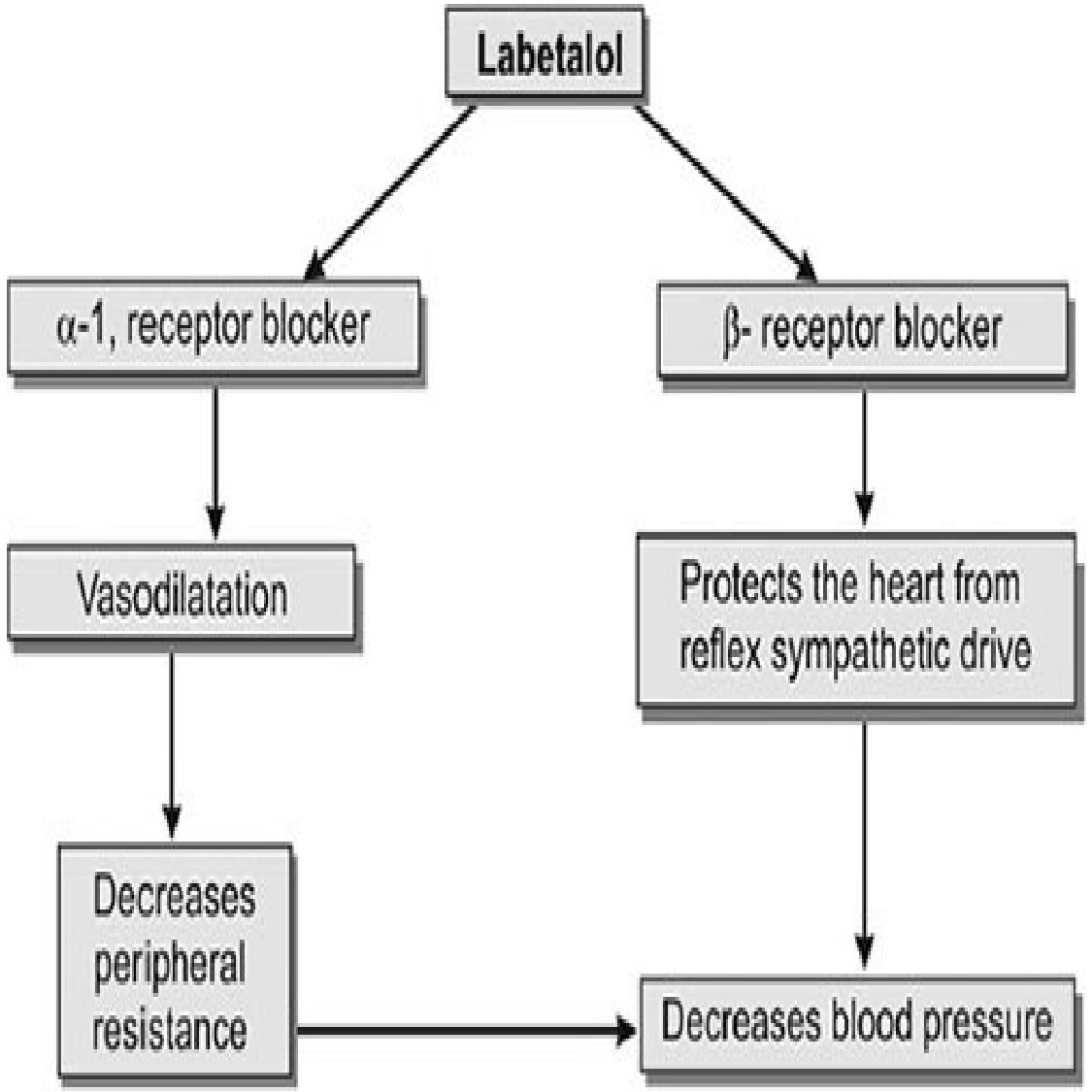
- *It* is metabolized rapidly (half-life of minutes) and so used ONLY by IV infusion by infusion pump
- Use Fresh Solution.
- Cover with Foil (Photosensitive).
- Continuous monitoring.
- Never stop infusion suddenly.

How to prevent cyanide toxicity

- Administration of sodium thiosulfate as a sulfur donor facilitates metabolism of cyanide to thiocyanate.
- Hydroxocobalamin combines with cyanide to form the nontoxic cyanocobalamin (a form of vitamin B_{12}).
- Both may be used for prophylaxis or treatment of cyanide poisoning during nitroprusside infusion.

2. Labetalol

- *Labetalol* is both an α- and β-blocker
- Given as an intravenous bolus or infusion in hypertensive emergencies.
- *Labetalol* does not cause reflex tachycardia.
- Used in pheochromocytoma and hypertension with pregnancy



3. Fenoldopam

- *Fenoldopam* is a **peripheral dopamine-1** receptor agonist that is given as an intravenous infusion.
- It maintains or increases renal perfusion while lowering blood pressure.
- It relaxes mainly the renal (renal artery, afferent and efferent arterioles) and mesenteric arterial vessels.
- The diuretic action of *fenoldopam* is mainly caused by the increase in renal blood flow.
- It can be safely used in all hypertensive emergencies and may be particularly beneficial in patients with renal insufficiency.
- . As with other direct vasodilators, the major toxicities are reflex tachycardia, headache, and flushing.

4. Nicardipine

- *Nicardipine*, a calcium-channel blocker
- given as **an intravenous infusion.**

5. Diazoxide

- **A potassium channel opener** that causes hyperpolarization in smooth muscle cells arteriolar dilating property,
- It was formerly used **parenterally** to treat hypertensive emergencies.
- Diazoxide inhibits insulin release from the pancreas (probably by opening potassium channels in the beta cell membrane) and so it is used () to treat hypoglycemia secondary to insulinoma. **orally**

Centrally acting alpha agonists	Stimulate α2 receptors in brainstem, reducing sympathetic outflow

Beta adrenergic blocking agents	Block cardiac β1 adrenergic receptors, reducing heart rate and cardiac contractility

Angiotensin converting enzyme inhibitors	Block conversion of angiotensin I to angiotensin II,a potent vasoconstrictor
Angiotensin II receptor blockers	Competitively block angiotensin II receptors
Dihydropyridine calcium channel blockers	Bind α1 subunit of L-type calcium channel in muscle cell membrane, reducing vascular smooth muscle contractility
Director vasodilators	Hydralazine reduces intracellular calcium in vascular smooth muscle cells and minoxidil causes potassium efflux with smooth muscle relaxation; both drugs cause arteriolar dilation

Thiazide diuretics	Inhibit Na-Cl cotransporter in distal convoluted tubule of nephron, causing natriuresis
Loop diuretics	Inhibit Na-K-Cl cotransporter in loop of Henle of nephron, causing natriuresis
Mineralocorticoid receptor blockers	Competitively inhibit aldosterone binding to the mineralocorticoid receptor, ultimately reducing sodium reabsorption in collecting duct of nephron

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Lecture Quiz

Question 1: Which of the following antihypertensives may cause cyanide toxicity

a) Labetalol

b) Na nitroprusside

c) Fenoldam

d) Prazosin

e) Nifedipine

Lecture Quiz

Question 2: Explain role of fenoldam in treatment of hypertensive emergency

Lecture Quiz

Question 3: Which diuretic may be used in renal impairment
a) Spironolactone b) Thiazides c) Fruzemide

Question 4 : List side effects of captopril

Question 5 : compare mechanism of action between prazosin and nifedipine

SUGGESTED TEXTBOOKS

1. Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2. Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.